REMARKS

Rejections for obviousness-type double patenting

Claims 1-5, 8, 10-12, 14-16, 20-21 and 23 have been rejected under the judicially created doctrine of obviousness-type double patenting in view of claims 1, 2, 4-7, 12-13, and 15-19 of U.S. Pat. No. 5,952,176 in view of Landegren (Technical Focus, 1993). The Examiner asserts that the only difference between the claims of the instant application and indicated claims of the '176 patent is the extension of the released upstream DNA fragment with a template nucleic acid and analyzing the resultant fragments. The Examiner relies on Landegren (1993) for supporting that in vitro amplification reactions of DNA to make the detection of the target DNA more sensitive, were well known at the time of the invention. Applicants traverse this rejection and withdrawal thereof is respectfully requested.

The Examiner acknowledges that the indicated claims of the '176 patent do not have the features of the present invention of extension of the released upstream fragment as a template nucleic acid and analyzing the resultant fragments. The Examiner's evaluation of the '176 patent is correct in this regard. However, the Examiner then takes the view that it would have been obvious to further amplify the DNA in order to improve the sensitivity of the method based on the teachings of Landegren (1993), page 199. The

Landegren article does, indeed, generally outline the advantages of using amplification techniques to improve sensitivity. However, increased sensitivity is not the major problem overcome with the present invention.

The crux of the problem solved by the present invention concerns the generation of the extendible upstream DNA fragment and incubating the extendible upstream fragment in the presence of an enzyme allowing for extension of the extendible fragment, such as a DNA polymerase, and a template nucleic acid; and analyzing the resultant fragments.

The Examiner's evaluation of the invention in view of the references appears to overlook an essential feature of the invention. Landegren (1993) is a general review of DNA amplification methods. In the DNA amplification methods reviewed in the Landegren publication (as in all publications relating to amplification prior to the invention), it was taught that a primer can be extended on a template in a cyclical fashion. Extension of a primer on a template was very well known in the prior art.

The current invention, on the otherhand, provides a method for generating an extendible upstream DNA fragment (steps i) to iii)), which in a sense is a primer, and the interrogation of the nature of the 3' end of the primer by analyzing the nature of the extension, or lack thereof, on a template nucleic acid (step iv)).

The information generated in the process of the invention allows the investigator to determine the nature of the 3' end of the extendible fragment and so generate diagnostic information regarding the 3' end of the extendible fragment, which directly relates to the DNA from which the extendible fragment was generated (in step i)). As a result, the present invention thus provides diagnostic information on the original DNA molecule in which the modified base was introduced.

Thus, the problem overcome in Landegren (1993), i.e. the use of amplification to increase sensitivity, has nothing to do with the problem overcome with the present invention. The present invention is not concerned with further amplification of the extendible fragment to allow more sensitive detection as indicated by the Examiner in relation to Landergren (1993). As discussed above, Landegren (1993) only teaches the extension of primers on a template nucleic acid and cyclical extension, which is amplification. The primers of Landegren (1993) are not analyzed by examining their ability to extend on a template nucleic acid. In the typical prior art at the time of the invention (such as Landegren (1993)), the nature of the template was analyzed by examining the nature of the extension of the primers on the template. The present invention is very different from the prior art, as the nature of the generated extendible fragment is instead

interrogated by examining the nature of its extension on a template. There is no suggestion of this feature in Landegren (1993). As such, the present invention is not achieved by combining the indicated claims of the '176 patent with the teachings of Landegren (1993) and the present invention is not obvious over the combined references. Withdrawal of the obviousness-type double patenting rejection is therefore respectfully requested.

Rejections under 35 U.S.C.§102(b)

Claims 1-21 and 23 have been rejected under 35 U.S.C.§102(b) as being anticipated by Dianov et al. (1992). Applicants traverse this rejection and withdrawal thereof is respectfully requested. The Examiner relies on Figure 1 at page 1606 of Dianov for allegedly teaching the recited steps of the present invention and at page 1605 for teaching that the excision is typically with a DNA deoxyribophosphodiesterase. However, as noted previously Applicants have never contested or asserted the novelty of cleaving at an abasic site to generate a 3'OH terminus.

Cleavage at abasic sites and generation of 3'OH termini was known at the time of the present invention. Applicants have not in the past, and are not now, asserting the invention of cleavage at abasic sites to generate a 3'OH terminus. Dianov fails to disclose

the present invention and the present invention differs from the teachings of Dianov in at least two aspects.

Dianov et al. describe a method of determining the repair gap in DNA following action by DNA glycosylases and endonucleases to repair damaged DNA. The process described in Dianov et al. demonstrates the insertion of 1-2 nucleotides and the closing of the gap in the DNA. The process of Dianov et al. necessarily requires the incorporation of 1-2 nucleotides by polymerase action of a downstream processing dRpase or enxonuclease activity, which is not required by the present invention. The present invention, on the other hand, involves the extension of the upstream fragment, i.e. the released extendible upstream DNA fragment, in the presence of an enzyme that allows for such extension and which may be a polymerase or a ligase, to a length determined by the additional/new template used to drive the reaction and/or the nucleotides supplied for the reaction.

A second difference between the present invention and the reference lies in the fact that Dianov et al. only disclose cleavage on the 5′ side, followed by action of 5′ dRpase or 5′ to 3′ exonuclease. The present method, on the other hand, involves the cleavage of the DNA at the abasic site following excision of the modified base. In the present method, cleavage can be either on the 3′ or the 5′ side of the abasic site. Cleavage on the 3′

side of the abasic site is followed by the subsequent cleavage of the 3′ dRp moiety on the upstream fragment to generate a 3′ OH group, if necessary.

As such, the present invention as claimed is distinguished from Dianov and withdrawal of the rejection is respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact MaryAnne Armstrong, PhD (Reg. No. 40,069) at the telephone number of the listed below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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